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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,319	08/19/2003	Michael D. Ruff	019031-000010	3826

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EXAMINER	
BERKO, RETFORD O	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,319	RUFF ET AL.	
	Examiner	Art Unit	
	Retford Berko	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/21/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement: The Information Disclosure Statement filed October 21, 2003 is acknowledged.

Claim Rejections - 35 USC § 112

Claim 12 and 15 recite the limitation "the process of claim 1, further including encapsulating the resultant" in a gelatin capsule. There is insufficient antecedent basis for this limitation in the claim because in the independent claim 1, no mention is made of a resultant tablet.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 2, 3, 4, 30, 31 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al (US 4, 910, 021).

The claims are directed toward a process for making a pharmaceutical formulation for oral administration wherein the active ingredient is a peptide pharmaceutical and process comprises applying a solution of the active ingredient to form a coating on a particulate pharmaceutical substrate wherein the substrate is free of a polysaccharide.

2. As in claims 1 and 2, Davis et al (Patent '021) teaches a method of making a pharmaceutical formulation for oral administration (i.e. capsule) comprising pharmaceutically active ingredients such as insulin, calcitonin and human growth hormone; such capsule coated

with film-forming composition such as ethyl cellulose (abstract, col 6, lin 5-15, col 4, lin 40-48 and col 7, lin 15-25).

3. As in claim 3, Patent '021 teaches an excipient and ethyl cellulose in the compostition (col 2, lin 15-20 and col 4, lin 45-50).

4. As in claim 4, Patent '021 teaches a permeation enhancer, also called drug absorption promoter (col 2, lin 15-20).

5. As in claim 55, Patent '021 teaches a composition for oral administration comprising insulin as active ingredient (approx. 0.3% wt/wt; see examples 4 and 7 at col 6, lin 5-40).

6. As in claims 1, 30 and 31; Patent '021 teaches a process for forming the particulate composition (col 7, lin 11-33).

7. Claims 1, 2, 3, 4, 30, 31 and 55 are anticipated by Patent '021.

8. Claims 1-7, 14 and 16-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Friend et al (US 5, 811, 388).

9. As in claim 1 and 16-22 Friend et al (Patent '388) teaches a process for making a pharmaceutical composition for oral administration (tablet) comprising active ingredient, core in which the active ingredient is concentrated and a layer surrounding the core (abstract, col 5, lin 45-55).

10. As in claim 2, Patent '388 teaches that the active drug in the core is a peptide drug, e.g. growth hormone (col 4, lin 60-65, col 9, lin 10-45) or insulin (col 9, lin 10-20).

11. As in claim 3, Patent '388 teaches a coating agent (col 4, lin 1-10) or excipients (col 3, lin 65 and col 11, lin 24-45).

12. As in claim 4, Patent '388 teaches film-coating (col 14, lin 10) and the use of film-formig polymers, e.g. ethylcellulose (col 12, lin 20-25).

13. Patent '388 teaches the limitation in claim 5 the weight of the active ingredient in the tablet is 0.01-10% wt/wt (abstract and col 27, lin 10).

14. As in claim 6-7, Patent '388 teaches the use of calcium phosphate as the substrate (col 12, lin 1-15). Claims 14, 16-22 recite the limitations of claims 1-7 in essence.

15. Claims 1-7, 14 and 16-22 are anticipated by Patent '388.

Claim Rejections-35 USC Sec. 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The relevant part of the factual inquiries set forth in Graham v. John Deere & Co., 383 U.S. 1, 148 USPQ 459 (1966) that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and content of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue
3. Resolving the level of ordinary skill in the pertinent art
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

17. Claims 1-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis (US 4, 910, 021) in view of Friend (US 5, 811, 388) further in view of Urist (US 4, 596, 574).

18. The claims are directed toward a process for making a pharmaceutical formulation for oral administration wherein the active ingredient is a peptide pharmaceutical (e.g. human insulin, animal insulin or a mixture thereof: the human insulin comprises of hexyl insulin monoconjugate-2-polydisperse) and process comprises applying a solution of the active ingredient to form a coating on a particulate pharmaceutical substrate wherein the substrate is free of a polysaccharide.

The claims are also directed toward the pharmaceutical formulation formed by the process being a tablet and having a peptide as active ingredient, that the pharmaceutical ingredients in the solution includes a controlled release agent or sustained release agent; that the coating agent is a film-forming polymer or a permeation enhancer and that the substrate is calcium carbonate or calcium citrate or calcium phosphate (0.1-30% wt/wt).

The claims are further directed toward a pharmaceutical formulation formed by the process as having the active agent compressed on particulate calcium phosphate and having a coating agent selected from ethylcellulose, permeation enhancer or surfactant.

19. Davis et al (Patent '021) discloses a method of making a pharmaceutical formulation for oral administration (i.e. capsule) comprising pharmaceutically active peptide hormones as ingredients (e.g.insulin, calcitonin and human growth hormone). Patent '021 discloses that the capsule is coated with film-forming composition such as ethyl cellulose (abstract, col 6, lin 5-15, col 4, lin 40-48 and col 7, lin 15-25). Patent '021 disclose the use of excipient and ethyl cellulose in the composition (col 2, lin 15-20 and col 4, lin 45-50). Patent '021 discloses the use of a permeation enhancer (drug absorption promoter; col 2, lin 15-20). More importantly, Patent '021 disclose that the composition formed by the process is for oral administration and comprises

of porcine insulin as active ingredient (approx. 0.3% wt/wt; see examples 4 and 7 at col 6, lin 5-40 and col 9, lin 1-10).

20. Patent '021 does not disclose the use of calcium carbonate or calcium phosphate as substrate in making the particulate formulation.

21. Friend et al (Patent '388) discloses a process for making a pharmaceutical composition for oral administration in the form of tablet comprising active ingredient, core in which the active ingredient is concentrated and a layer surrounding the core (abstract, col 5, lin 45-55). Patent '388 discloses that the active drug in the core is a peptide drug, e.g. growth hormone (col 4, lin 60-65, col 9, lin 10-45) or insulin wherein the % of insulin wt/wt is 0.01-10% (abstract; col 9, lin 10-20 and col 27, lin 10). Patent '388 discloses a coating agent (col 4, lin 1-10) or excipients (col 3, lin 65 and col 11, lin 24-45). Patent '388 discloses film-coating (col 14, lin 10) and the use of film-formig polymers, e.g. ethylcellulose (col 12, lin 20-25). More significantly, Patent '388 discloses the use of calcium phosphate as the core substrate for formation of the oral delivery composition (col 12, lin 1-15).

22. Urist (Patent '574) discloses a drug delivery system comprising bone morphogenic protein (BMP) in the form of a porous ceramic delivery system that can provide sustained delivery of the bioactive BMP to bone tissue; wherein the ceramic substance is tricalcium phosphate (abstract, col 2, lin 5-25) and col 6, lin 5-25). Though Patent '574 does not disclose the specific oral administration of the system, Patent '574 discloses the use of the system as an implant or as prosthesis device for slow release of BMP to bone (abstract, col 3, lin 65)—this use can include oral tissue as well.

23. One of ordinary skill in the art would be motivated to prepare particulate composition comprising active agents such as peptide growth hormone, insulin, etc. using the procedures disclosed in the cited prior art. By coating the particulate composition with enteric coating layer (s), one of ordinary skill would expect to obtain an effective bioactive agent because the agent such as insulin or other peptide hormones that are normally very unstable would be protected from the inactivating environment of the stomach by the film coating applied thereon. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill at the time it was made.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Retford Berko** whose telephone number is 571-272-0590. The examiner can normally be reached on M-F from 8.00 am to 5.30 pm

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Thurman K Page**, can be reached on 571-272-0602.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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SUPERVISORY PATENT EXAMINER
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